Efficacy of rituximab on pulmonary nodulosis occurring or increasing in patients with rheumatoid arthritis during anti-TNF-α therapy

Sirs,

We describe a series of 3 RA patients in whom anti-TNF-α therapy was associated with the development of pulmonary nodules, or with the increase – in terms of number and size – of previously-existing nodules.

In all patients, the interruption of anti-TNF-α therapy and the subsequent administration of rituximab (1000 mg followed by 1000 mg 2 weeks later) were associated with a reduction in the number and in the size of rheumatoid nodules: moreover previously-excavated nodules became solid.

Patient 1 is a 61-year-old woman with a 6-year history of seropositive RA without significant pleuro-parenchymal alterations (Rx). In June 2007, adalimumab (ADA) was added to leflunomide (LEF) therapy. In September 2007 a HRCT showed the presence of an excavated subpleural nodule (Fig. 1A). ADA therapy was interrupted and several diagnostic assessments excluded neoplastic or infections lesions. In January 2008 a HRCT showed unchanged nodular lesion but as an increase of disease activity was observed, we decided to add rituximab. In March 2008 the disease activity appeared low and a new HRCT showed a reduction in the size of nodule and the absence of cavities (Fig. 1B).

Patient 2 is a 60-year-old woman with seropositive early RA and pulmonary rheumatoid nodules (HRCT). In June 2008, etanercept (ETN) was commenced in combination with LEF and the disease activity reduced. In September 2008 a new HRCT showed an enlargement and the excavation of some lesions. ETN was discontinued. In December 2008 a new HRCT was similar to previous HRCT. Due to ongoing disease activity rituximab was initiated. In March 2009 all bilateral nodules were reduced in size: the nodule at the right upper lobe, which was previously excavated, appeared solid.

Patient 3 is a 72-year-old man with seropositive RA and pulmonary rheumatoid nodules (biopsy). In June 2008 ETN was added to methotrexate. In December 2008 a HRCT documented an increase in the size of pulmonary nodules and an excavation of a nodule. ETN was discontinued. Four months after a new HRCT did not show any variation. We started treating the patient with rituximab. In September 2009 a HRCT showed a marked reduction in size of parenchymal nodules: the excavated nodule appeared solid.

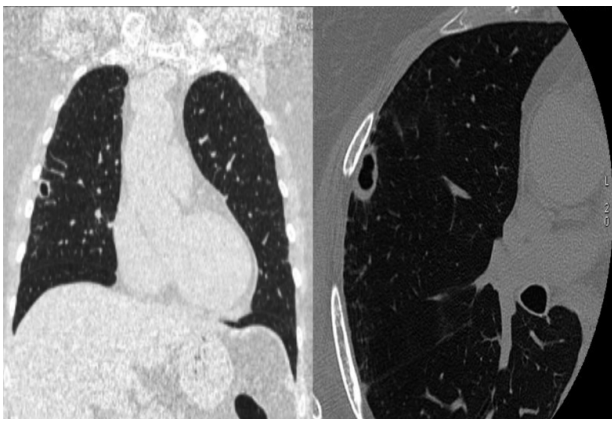
Several reports have documented the onset of pulmonary nodulosis in RA patients treated with anti-TNF-α (1-7). On the other hand, Derot has reported a reduction in number and size of rheumatoid lung nodules following ETN therapy (8) and Baeten has documented the lack of a histopathologic effect by infliximab on rheumatoid nodules (9).

These data suggest that the mechanism underlying the development of rheumatoid nodulosis is, at least in part, TNF-α-independent and that the effects of anti-TNF-α agents may change the immunopathological processes TNF-α-independent. This hypothesis may justify the development of extra-articular manifestations of RA and the onset of autoimmune manifestations not directly associated with RA (11-12).

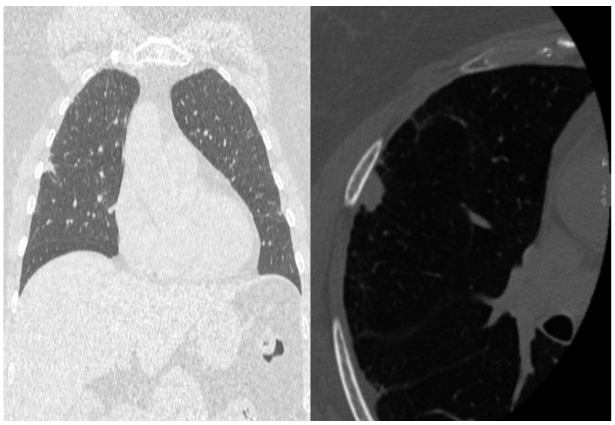
In the three patients with seropositive RA described in the present case series, anti-TNF-α therapy was effective in the control of rheumatoid synovitis, but was associated with the onset and/or with the worsening of pulmonary rheumatoid nodules. Three months after the withdrawn of anti-TNF-alpha therapy, in our patients, the pulmonary nodules have not shown spontaneous regression. However, we cannot be certain that the observed following regression of pulmonary nodules are actually promoted by either the interruption of anti-TNF-α therapy or the subsequent initiation of rituximab. In any case, the present case report documents a lack of worsening of rheumatoid nodules with rituximab administration. To date, information on the effects of rituximab on rheumatoid nodules is still scant. To our knowledge, a single case documented the control of lung nodulosis with rituximab therapy (10).

The absence of worsening of rheumatoid nodules associated with rituximab could have high clinical relevance. In fact, the presence of pulmonary nodules in immunocompromised patients, like those affected from RA and treated with biological drugs, poses a diagnostic and therapeutic challenge as it could be due to infectious or non-infectious causes.

Fig. 1.
A. High-resolution CT scanning of the lungs during adalimumab treatment showed the presence of an excavated sub-pleural nodule with sclerotic edge (diameter 1.6–1.1 cm) at the middle-lobe level.



B. After rituximab treatment the CT of the lung showed a reduction in the size of nodule and the absence of cavitation.



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